

General

Guideline Title

Practice advisory: etanercept for poststroke disability: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology.

Bibliographic Source(s)

Gronseth GS, Messing SR. Practice advisory: etanercept for poststroke disability: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2016 Jun 7;86(23):2208-11. [17 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I-IV) are provided at the end of the "Major Recommendations" field.

Recommendation

Clinicians should counsel patients considering etanercept for treatment of poststroke disability that there is insufficient evidence to determine its effectiveness and that the treatment may be associated with adverse outcomes and high cost (Level U).

Definitions

Classification of Evidence Scheme for Therapeutic Studies

Class I

- Randomized, controlled clinical trial (RCT) in a representative population
- Masked or objective outcome assessment
- Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences
- Also required:
 - a. Concealed allocation
 - b. Primary outcome(s) clearly defined

- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
- e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
 - 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority
 - 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
 - 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment
 - 4. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers
- f. No more than 2 primary outcomes prespecified
- g. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate

Class II

- Cohort study meeting criteria b–e (see Class I) or an RCT that lacks 1 or 2 criteria a–e (see Class I)
- Randomized crossover trial missing 1 of the following 2 criteria:
 - a. Period and carryover effects described
 - b. Baseline characteristics of treatment order groups presented
- All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences
- Masked or objective outcome assessment

Class III

- Controlled studies (including well-defined natural history controls or patients serving as their own controls)
- Crossover trial missing both of the following 2 criteria:
 - a. Period and carryover effects
 - b. Baseline characteristics presented - an RCT that does not have relevant baseline characteristics presented that are substantially equivalent
- A description of major confounding differences between treatment groups that could affect outcome**
- Outcome assessment masked, objective, or performed by someone who is not a member of the treatment team

Class IV

- Did not include patients with the disease
- Did not include patients receiving different interventions
- Undefined or unaccepted interventions or outcome measures
- No measures of effectiveness or statistical precision presented or calculable

*Numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III

**Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

Classification of Recommendations

Assigning a Level of Strength to the Recommendation

When there is sufficient evidence to support an inference for the use of an intervention (i.e., the balance of benefits and harms favors the intervention), the author panel assigns one of three recommendation designations: A, B, or C. Each designation corresponds to a helping verb that denotes the level of strength of the recommendation. Level A is the strongest recommendation level and is denoted by the use of the helping verb *must*. *Must* recommendations are rare, as they are based on high confidence in the evidence and require both a high magnitude of benefit and low risk. Level B corresponds to the helping verb *should*. *Should* recommendations tend to be more common, as the requirements are less stringent but still based on the evidence and benefit–risk profile. Finally, Level C corresponds to the helping verb *may* or *might*. *May* and *might* recommendations represent the lowest allowable recommendation level the American Academy of Neurology (AAN) considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation.

Level A denotes a practice recommendation that "must" be done. In almost all circumstances, adherence to the recommendation will improve health-related outcomes. A Level B indicates a recommendation that "should" be done. In most circumstances, adherence to the recommendation will likely improve health-related outcomes. A Level C represents a recommendation that "might" be done. In some circumstances, adherence to the recommendation might improve health-related outcomes.

When there is insufficient evidence to support an inference for the use of an intervention (i.e., the balance of benefits and harms is unknown) a Level U or Level R designation is appropriate.

A Level U indicates that the available evidence is insufficient to support or refute the efficacy of an intervention. A Level R is assigned when the balance of benefits and harms is unknown and the intervention is known to be expensive or have important risks. A Level R designates that the intervention should not be used outside of a research setting. Non-evidence-based factors that need to be transparently and systematically considered when formulating recommendations include the following:

- The relative value of the benefit as compared with the risk; this is derived from consideration of:
 - The importance to patients of the health related-outcomes (both benefits and harms)
 - The size of the intervention's effect
 - The risk of harm of the intervention (i.e., tolerability and safety)
- The feasibility of complying with the intervention (e.g., the intervention's availability)
- The cost of the intervention
- The expected variation in patient preferences relative to the risks, burdens, and benefits of the intervention

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Poststroke disability

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Neurology

Intended Users

Physicians

Guideline Objective(s)

- To review evidence regarding the effectiveness, safety, and tolerability of etanercept used to treat patients with poststroke disability
- To address the following question: For adult patients with poststroke disability, does etanercept administered by any route (compared with no etanercept or placebo) improve functional status?

Target Population

Adult patients with poststroke disability

Interventions and Practices Considered

Etanercept

Major Outcomes Considered

- Efficacy of etanercept (change from pretreatment status after etanercept treatment on any measure of functional ability)
- Safety and tolerability of etanercept

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

In June 2013 and again in June 2015, the Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) performed a search of MEDLINE for articles published using the search terms "cerebrovascular disorders" and "etanercept." Search results were filtered through the broad therapeutic clinical query (see appendix e-3 of the online Data Supplement for the specific search strategy employed [see the "Availability of Companion Documents" field]). The Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials were also searched. A secondary search of the references of selected articles and review articles was performed to identify studies missed by the search strategy.

The titles and abstracts of the identified citations were reviewed for relevance to the clinical question. The full text of potentially relevant articles was retrieved and included in the analysis if the investigators determined functional status in patients with stroke who were treated with etanercept administered by any route. Studies in animals and those with non-English-language abstracts were excluded from the analysis.

Number of Source Documents

The search strategy identified 33 citations. Twenty-nine articles were excluded because they were review articles, did not specifically include patients with stroke, or were performed on animals. The full text of 4 potentially relevant articles was reviewed. One of these articles was a review without primary data, and one article was a case report of a patient without magnetic resonance imaging (MRI) evidence of a stroke. Two articles met inclusion criteria.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence Scheme for Therapeutic Studies

Class I

- Randomized, controlled clinical trial (RCT) in a representative population
- Masked or objective outcome assessment
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- Also required:
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 - c. Exclusion/inclusion criteria clearly defined
 - d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
 - e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority
 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment
 4. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers
 - f. No more than 2 primary outcomes prespecified
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- Cohort study meeting criteria b–e (see Class I) or an RCT that lacks 1 or 2 criteria a–e (see Class I)
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Class IV

- Did not include patients with the disease
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*Numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing the class is automatically downgraded to Class III

**Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

Methods Used to Analyze the Evidence

Description of the Methods Used to Analyze the Evidence

Both authors, along with members of the American Academy of Neurology (AAN) GDDI, independently reviewed articles and completed data abstraction forms. Discrepancies were resolved through discussion.

The investigators determined acceptable effect measures to be a change from pretreatment status after etanercept treatment on any measure of functional ability. When possible, 95% confidence intervals (CIs) were used as the measure of statistical precision.

Studies were rated for their risk of bias using the American Academy of Neurology (AAN) 4-tiered classification of evidence scheme for therapeutic studies (see the "Rating Scheme for the Strength of the Evidence" field). After anchoring to the risk of bias rating, the advisory authors rated the overall confidence in the evidence using a modified Grading, Recommendations Assessment, Development and Evaluation process (see appendix e-5 in the online Data Supplement [see the "Availability of Companion Documents" field]).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) developed the wording of actionable recommendations and determined the strength of the recommendations after considering the strength of evidence and deductive inferences, risks and benefits, cost, feasibility, and patient preferences (see appendix e-6 in the online Data Supplement [see the "Availability of Companion Documents" field]).

Rating Scheme for the Strength of the Recommendations

Assigning a Level of Strength to the Recommendation

When there is sufficient evidence to support an inference for the use of an intervention (i.e., the balance of benefits and harms favors the intervention), the author panel assigns one of three recommendation designations: A, B, or C. Each designation corresponds to a helping verb that denotes the level of strength of the recommendation. Level A is the strongest recommendation level and is denoted by the use of the helping verb *must*. *Must* recommendations are rare, as they are based on high confidence in the evidence and require both a high magnitude of benefit and low risk. Level B corresponds to the helping verb *should*. *Should* recommendations tend to be more common, as the requirements are less stringent but still based on the evidence and benefit–risk profile. Finally, Level C corresponds to the helping verb *may* or *might*. *May* and *might* recommendations represent the lowest allowable recommendation level the American Academy of Neurology (AAN) considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation.

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A Level U indicates that the available evidence is insufficient to support or refute the efficacy of an intervention. A Level R is assigned when the balance of benefits and harms is unknown and the intervention is known to be expensive or have important risks. A Level R designates that the intervention should not be used outside of a research setting. Non-evidence-based factors that need to be transparently and systematically considered when formulating recommendations include the following:

- The relative value of the benefit as compared with the risk; this is derived from consideration of:
 - The importance to patients of the health related-outcomes (both benefits and harms)
 - The size of the intervention's effect

- The risk of harm of the intervention (i.e., tolerability and safety)
- The feasibility of complying with the intervention (e.g., the intervention's availability)
- The cost of the intervention
- The expected variation in patient preferences relative to the risks, burdens, and benefits of the intervention

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Drafts of the practice advisory have been reviewed by at least three American Academy of Neurology (AAN) committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields.

A draft of the practice advisory was made available for public comment from January 28, 2014, through February 28, 2014. The draft manuscript was modified in response to some of the comments.

The practice advisory was approved by the Guideline Development, Dissemination, and Implementation Subcommittee on November 7, 2015; by the Practice Committee on November 19, 2015; and by the AAN Institute Board of Directors on February 11, 2016.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for the recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Two case series were identified, and both reported clinical improvements 3 weeks following treatment across a wide range of functional domains. However, both studies were rated Class IV because of poor methodologic quality (i.e., high risk of bias). The advisory authors have very low confidence in the evidence for efficacy of etanercept for poststroke disability because of the high risk of bias of the relevant studies. The biological plausibility of benefit was judged to be low because of the reported immediate onset of benefit and single administration of a transiently acting medication. Explanations other than the effectiveness of the treatment for the observed improvements include observer expectation, performance motivation, regression to the mean, and the placebo effect.

Potential Harms

Although adverse events of etanercept were not described in the studies reviewed for this practice advisory, serious adverse events are described in studies of patients receiving etanercept for other conditions. Such events include injection site reactions, reactivation of tuberculosis, reactivation of hepatitis B virus infection, congestive heart failure, demyelinating neurologic disorders, vasculitis, and hematologic disorders such as aplastic anemia and pancytopenia. A recent randomized trial of subcutaneous etanercept 50 mg once weekly for 24 weeks for the treatment of Alzheimer

disease reported no significant difference in the adverse event rates between patients treated with placebo and patients treated with etanercept. However, the study lacked the statistical precision to exclude uncommon, potentially serious adverse events. It is unclear whether the adverse event profile resulting from the recurrent use of etanercept can be generalized to the time-limited perispinal administration used for the treatment of poststroke disability. Given the limitations of the efficacy of the evidence and the potential for serious adverse events, the advisory authors judged the risk-benefit tradeoffs of etanercept for poststroke disability to be unfavorable.

Qualifying Statements

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Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Gronseth GS, Messé SR. Practice advisory: etanercept for poststroke disability: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2016 Jun 7;86(23):2208-11. [17 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Jun 7

Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

Source(s) of Funding

This practice advisory was developed with financial support from the American Academy of Neurology (AAN). Authors who serve as AAN subcommittee members or methodologists (G.S.G., S.R.M.) were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

Guideline Committee

Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) of the American Academy of Neurology

Composition of Group That Authored the Guideline

Guideline Authors: Gary S. Gronseth, MD; Steven R. Messé, MD

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Financial Disclosures/Conflicts of Interest

Conflict of Interest

The American Academy of Neurology (AAN) is committed to producing independent, critical, and truthful practice advisories. Significant efforts

are made to minimize the potential for conflicts of interest to influence the recommendations of this practice advisory. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the practice advisories and the developers of the practice advisories. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, practice advisory projects. Drafts of the practice advisory have been reviewed by at least 3 AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com . For complete information on this process, access the 2011 AAN process manual.

Disclosures

G. Gronseth serves as an associate editor for *Neurology* and as an editorial advisory board member of *Neurology Now*, and receives compensation from the AAN for work as the chief evidence-based medicine methodologist. S. Messé is the vice-chair of the Guideline Development, Dissemination, and Implementation Subcommittee of the AAN; has received consulting fees from GlaxoSmithKline for protocol development; has received research support from Glaxo-SmithKline, W.L. Gore & Associates, and the NIH for clinical trials; and has received royalties from UpToDate for published articles. Go to Neurology.org for full disclosures.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

A list of American Academy of Neurology (AAN) guidelines, along with a link to this guideline, is available from the [AAN Web site](#) .

Availability of Companion Documents

The following are available:

- Practice advisory: etanercept for poststroke disability; report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Data supplement. St. Paul (MN): American Academy of Neurology; 2016. 7 p. Available from the [Neurology Journal Web site](#) .
- Practice advisory: etanercept for poststroke disability. ANN summary of practice advisory for clinicians. St. Paul (MN): American Academy of Neurology; 2016. 2 p. Available from the [American Academy of Neurology \(AAN\) Web site](#) .
- Brodtmann A, Kalra L. Experimental treatments for poststroke disability: hasten slowly. Editorial. *Neurology*. 2016 Jun 7;86(23):2122-2123. Available from the [Neurology Journal Web site](#) .
- American Academy of Neurology (AAN). Clinical Practice Guideline Process Manual, 2011 Ed. St. Paul (MN): American Academy of Neurology. Available from the [AAN Web site](#) .

Patient Resources

The following is available:

- Etanercept for poststroke disability. AAN summary of practice advisory for patients and their families. St. Paul (MN): American Academy of Neurology; 2016. 1 p. Available from the [American Academy of Neurology \(AAN\) Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on October 18, 2016. The information was verified by the guideline developer on November 15, 2016.

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